Program Announcements (PA'S)

RESEARCH IN PAGET'S DISEASE OF BONE

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

BACKGROUND

Paget's disease of bone, also known as osteitis deformans, is a chronic disease of the skeleton characterized by abnormally rapid bone turnover. Excessive bone breakdown and formation can result in bone that is dense but fragile. Paget's disease most frequently occurs in the bone of the spine, skull, pelvis, thighs, and lower legs. In more severe cases there may be secondary involvement of tissues other than bone.

As many as 3 million Americans over the age of 40 years have some form of Paget's disease of bone. Approximately 250,000 cases are severe enough to require medical intervention. The condition often develops progressively, and is most commonly diagnosed between the ages of 50 and 70.

Several laboratory tools are now available to confirm more clearly the diagnosis of Paget's disease. These include biochemical assays of blood for metabolic factors related to bone turnover, x-rays, bone scans, and bone biopsy. Some of the possible treatments available to alter bone metabolism for specific patients include human and salmon calcitonin, disodium etidronate and mithramycin. Other symptomatic relief may be available to patients. A few new therapies are under investigation at this time.

While the prognosis for Paget's disease has improved over the past 10 years, the etiology remains a mystery. In addition, none of the current treatment regimens is ideal for all patients.

GOALS AND SCOPE

This solicitation is intended to stimulate research that provides further understanding of Paget's disease of bone. Both basic and clinical research are encouraged. In some instances, collaborative and multi-disciplinary investigative efforts may be required to achieve significant scientific advances.

The NIH urges applicants for grants to give added attention where feasible and appropriate to the inclusion of minority groups and/or women in the study populations for research.

The NIAMS invites grant applications including, but not limited to, the following general areas:

Etiology

Virus-like nuclear and cytoplasmic inclusions have been found in the osteoclasts of Paget's disease patients. It is important to determine if these viruses have a role in the pathogenesis of Paget's or are an epiphenomenon unrelated to the course of the disease. (If a causative agent is found, does it provide a continuous stimulus or a single system perturbation?)

Because of numerous agents involved in the complex regulation of bone turnover in normal and Paget's bone, it would be valuable to isolate specific local and systemic factors that may be altered in the disease state. Investigations should seek to explain the increased regional angiogenesis present in Pagetic bone.

Genetics

Paget's disease follows familial and racial patterns that may be genetically based. HLA-linkage studies should be continued in families with a high prevalence of Paget's. Molecular biology techniques may uncover defects that make these kindreds unusually susceptible to developing this disease.

Bone Cell Biology

In a general sense it is valuable to evaluate further the phenotypic expression of Paget's cells. The basic structure and cell functioning of Pagetic bone needs more scientific study. The increased turnover rate of Paget's bone cells also makes them a potentially good model system for studies on basic bone cell biology.

Paget's disease results in a large increase in multinucleate osteoclasts which also develop increased numbers of calcitonin receptors. Therefore, important areas of future investigation include studying the generation of multinucleate osteoclasts from precursors and the special process of cell fusion. The calcitonin receptor should be cloned to allow further mechanistic evaluation of this multinucleate process.

It is not certain that the primary lesion in Paget's disease is in the osteoclast. The turnover imbalance may be driven by a defect in the osteoblast. The functional role of osteoblasts in Paget's disease requires further investigation.

Clinical Studies

Because many clinical studies of new drug therapies are currently being supported by pharmaceutical companies, clinical trials that duplicate these efforts are discouraged. However, new and unique approaches for treating the primary metabolic bone disorders or other secondary symptoms are appropriate in small-scale clinical evaluations.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures for research grants (Study Section). Review criteria include: significance and originality of the research goals and approaches; feasibility of the research and adequacy of the experimental design; training, research competence, and dedication of the investigator(s); adequacy of available facilities; and provision for the humane care of animals. Decisions will be based on Initial Review Group and appropriate National Advisory Council recommendations. Applications should be submitted on form PHS-398, available in the business or grants office at most academic or research institutions, or from the Division of Research Grants, National Institutes of Health. Applications will be accepted in accordance with the dates of new applications on a continuing basis: February 1, June 1, October 1.

The phrase "RESEARCH IN PAGET'S DISEASE OF BONE" should be typed on line 2 of the face page of the application. The original and six copies should be sent or delivered to:

Grant Application Receipt Office
Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, Maryland 20892-4500

For further information, investigators are encouraged to contact the following individual:

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This program is described in the Catalog of Federal Domestic Assistance No.

13.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.